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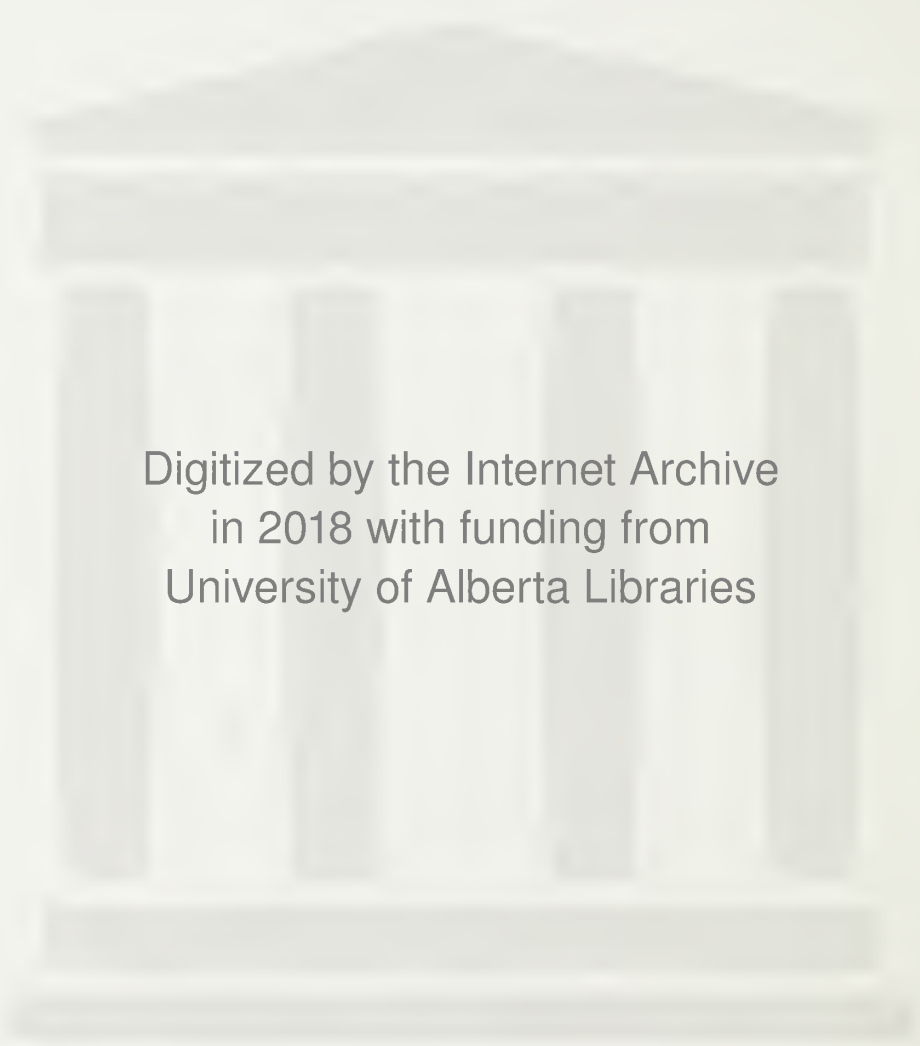
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AN INVESTIGATION OF SOME MONO-MERCURY
DERIVATIVES OF HALOGEN COMPOUNDS OF
FLUORESCEIN
and
THE PREPARATION OF β -AUROTHIOGLYCERIC
ACID ETHYL ESTER

by

Stanley Chaplin Lynn, B. Sc.

Department of Chemistry
University of Alberta

A THESIS

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Graduate Studies, University of
Alberta, in partial fulfilment
of the requirements for the
degree of Master of Science.

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The investigation described in this thesis was carried out in the Department of Chemistry of the University of Alberta.

The author wishes to express his gratitude to Dr. R. B. Sandin, for his helpful suggestions and assistance during the carrying out of this research.

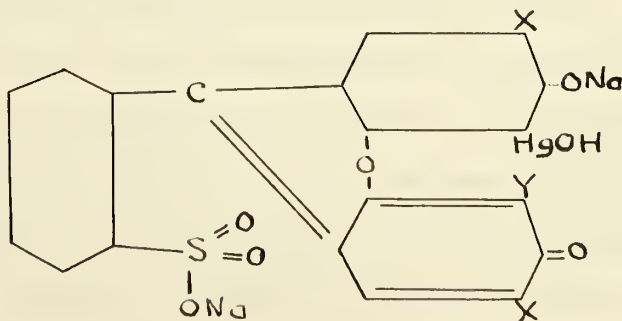
PART I

AN INVESTIGATION OF SOME MONO-MERCURY
DERIVATIVES OF HALOGEN COMPOUNDS OF
FLUORESCEIN
INTRODUCTION

The subject of this investigation was suggested by the report of W. E. Drake and F. Dunning¹, from the Bacteriological and Chemical Research Laboratories of Hynson, Wescott and Dunning.

In their investigation, they prepared the mono- and di-mercurated compounds of the dichloro, dibromo and di-iodoresorcinsulphonphthalein and determined from a bacteriological point of view the effect of the introduction of the different halogen atoms. A further objective of the research was to decide which member of the series showed the greatest bactericidal effect in therapeutic concentrations.

The sodium salts of these compounds were represented by the accompanying graphic formula:-



1. W. E. Drake and F. Dunning, J. Infect. Dis., 48, 367 (1931).

in which "X" denoted the position occupied by the halogen atoms respectively, chlorine, bromine or iodine. "Y" indicated the position occupied by the "HgOH" group in its di-mercury derivatives.

From their bacteriological examination of these compounds, they found, that resorcinsulphonphthalein was not bactericidal in a one percent solution; also the di-iodo derivative did not show any marked germicidal effect. However, the mono-mercury derivative of the parent substance showed a marked increase in bactericidal effect. The di-mercury compound was not greatly more active than the mono-mercury derivative and much more toxic.

When both mercury and halogen atoms were introduced into the molecule, a much greater bactericidal activity was observed, than when either of these atoms was introduced separately. Also, another interesting fact was disclosed, that the introduction of more mercury and more halogen atoms did not appear to result in a correspondingly greater increase in bactericidal value.

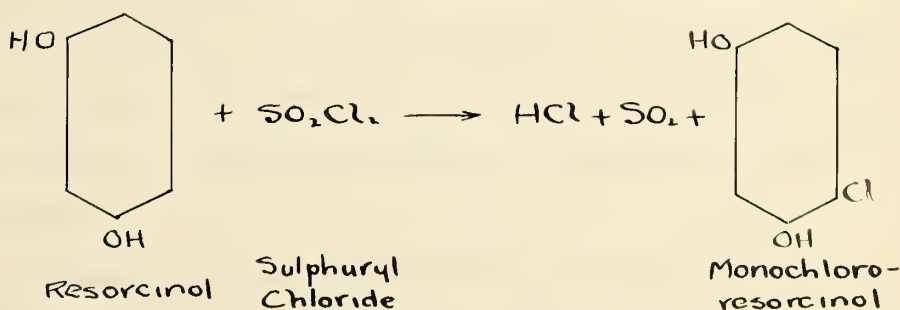
It was further found, in the investigation of compounds containing both mercury and halogen atoms, that the increase in bactericidal activity due to the introduction of bromine was greater than that due to the introduction of chlorine, and that in the same way, iodine induced a much greater increase than bromine. In other words, the increase in activity, due to the introduction of halogen atoms, followed the order of the elements in the Periodic Table.

Emil Klarmann and John Von Wövern², on investigating non-mercurated compounds containing chlorine and bromine atoms, found that the germicidal activity due to the introduction of chlorine was greater than that due to the introduction of bromine. That is, the increase in activity due to the introduction of halogen atoms, followed in the reverse order of the Periodic Table.

OUTLINE AND DISCUSSION OF INVESTIGATION

It was therefore decided to try to find out more regarding the relationship which exists between chemical constitution and bactericidal action. This investigation has to do with the preparation of halogenated fluoresceins and their mono-mercury derivatives.

The compound monochlororesorcinol was the starting point for the preparation of dichlorofluorescein. It was prepared by the method of Kolthoff³, in which one gram molecule of sulphuryl chloride was added to an ethereal solution containing one gram molecule of resorcinol.



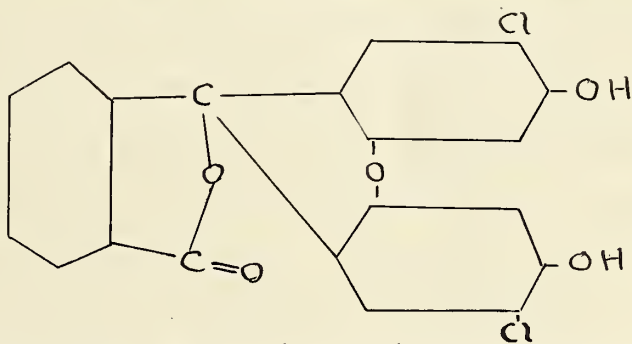
2. Emil Klarmann and John Von Wövern. J. Am. Chem. Soc. 51, 605(1929).

3. T. M. Kolthoff, W. M. Lauer and C. J. Sunde,

J. Am. Chem. Soc. 51, 3273 (1929).

Dichlorofluorescein was prepared by allowing one gram molecule of phthalic anhydride to react with two gram molecules of monochlororesorcinol. It was purified by converting it into the diacetate and then saponifying the diacetate with alcoholic potassium hydroxide, in accordance with the procedure used by I. M. Kolthoff, W. M. Lauer and C. J. Sunde³. Kolthoff and his collaborators³, attempted to prepare the dichlorofluorescein by the direct chlorination of fluorescein but all their attempts failed.

Kolthoff³ in his description of the compound, secured as above, assigned it the following formula, which is the lactoid structure.



In no place in the report did he give any analytical results on his final product. Also he described it as having an ochre-color, which contradicts the structure. Although the analysis of the diacetate was given, showing its purity, no mention was made of the melting-point.

In the investigation, Kolthoff³ was interested in the use of dichlorofluorescein as an absorption indicator for argentometric titration of chlorides. He desired to secure an indicator that would be more applicable than fluorescein for the titration of weakly acid solutions of low chloride concentration, since fluorescein

was only of use in weakly alkaline solutions. The indicator, to be better than fluorescein, had to have a larger dissociation constant and a greater adsorbability. He found that the introduction of chlorine atoms into the molecule produced the desired effect.

Our investigation showed that the material, so produced by Kolthoff's³ synthesis which he called dichlorofluorescein, was invariably low in chlorine content even after the most rigid drying up to 175°. The crude dichlorofluorescein thus obtained was acetylated giving the diacetate. This diacetate was recrystallized from benzene until the melting point was constant at 237° (uncorr.). It was then saponified according to Kolthoff³, but the material so produced was also invariably low in chlorine content.

W. R. Orndorff⁴ had similar difficulty in his investigation on eosin or tetrabromofluorescein. He obtained the colorless, lactoid form, $C_{20}H_8Br_4O_5$ by crystallizing the saponified tetrabromofluorescein diacetate from glacial acetic acid, and a red hydrate, $C_{20}H_8Br_4O_5 + 2.5H_2O$ by acidification of the cold alkaline solution of tetrabromofluorescein with acetic acid. At 150°, this red hydrate lost one and a half molecules of water and formed the rose-colored hydrate, $C_{20}H_8Br_4O_5 + H_2O$. Upon heating this hydrate to 276 - 281°, it was decomposed.

Gomberg⁵ in his investigation of erythrosin, or the di-sodium

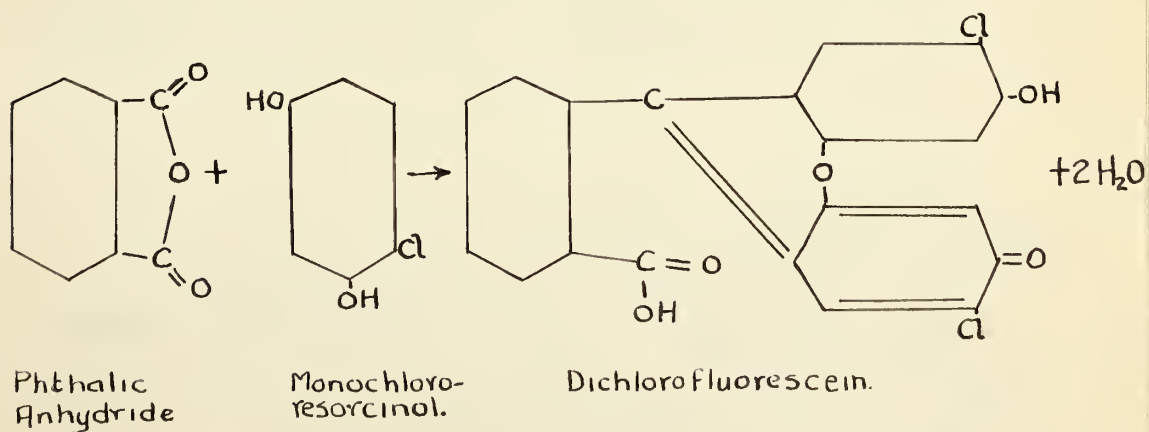
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4. W. R. Orndorff and A. J. Hemmer J. Am. Chem. Soc., 49, 1272 (1927).
 5. M. Gomberg and D. L. Tabern J. Ind. Eng. Chem., 14, 1115 (1922).

salt of tetra-iodofluorescein also had the same difficulty, that is, the compound seemed to hold very tenaciously to water.

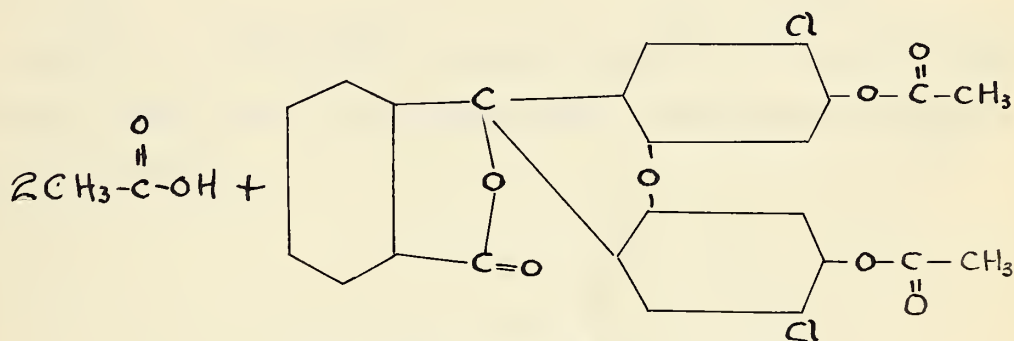
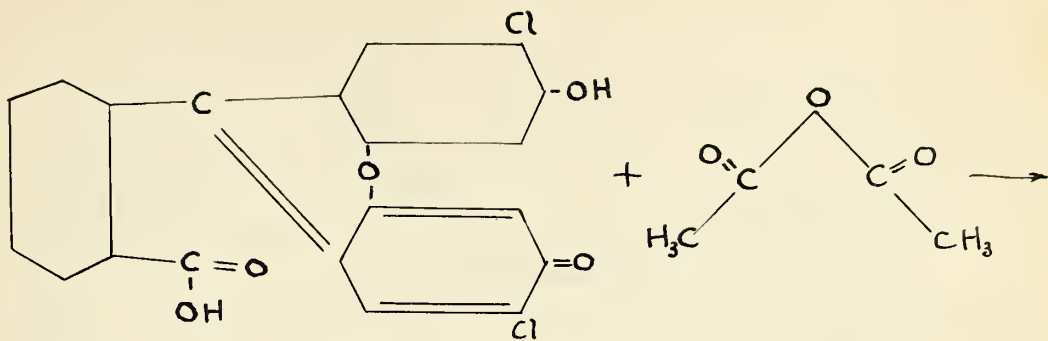
Therefore, following Orndorff's⁴ procedure, glacial acetic acid was tried as the solvent for the purification of dichlorofluorescein and was found to be quite efficient. It was noticed that, after each recrystallization of dichlorofluorescein from glacial acetic acid, the intensity of color decreased. The third recrystallization yielded a product having a very pale rose-color. The analysis of this compound indicated that it was pure dichlorofluorescein. The lactoid structure was given to this compound due to its light color.

Upon heating the light-colored crystals to 275 - 300°, glistening dark-red crystals were obtained. This indicated a transformation of original lactoid, light-colored, dichlorofluorescein to the quinoid modification.

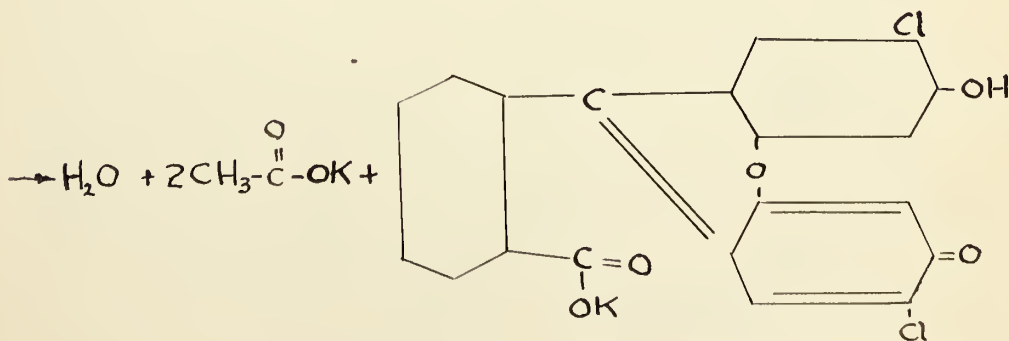
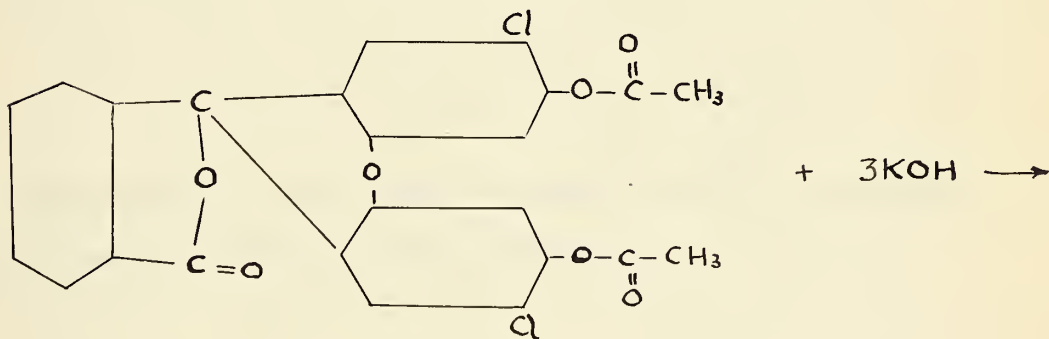
The reactions of the formation of dichlorofluorescein are given below:-

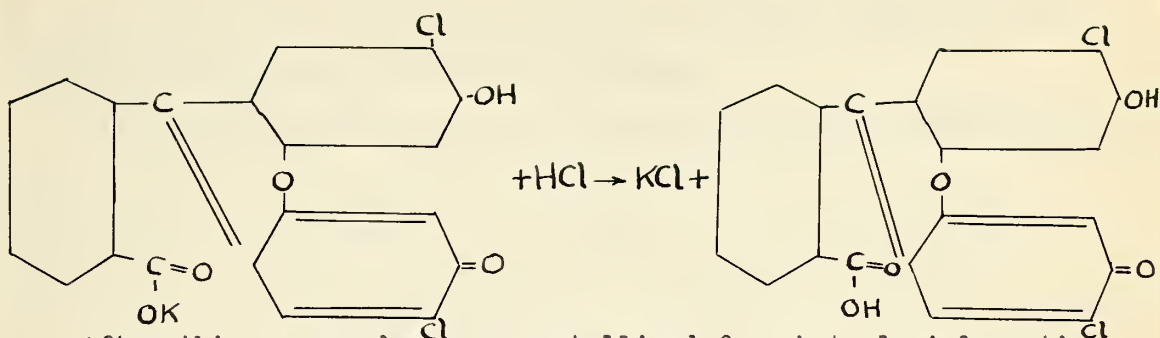




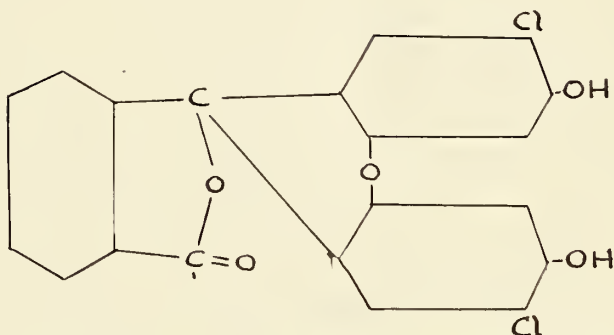


Dichlorofluorescein Diacetate.

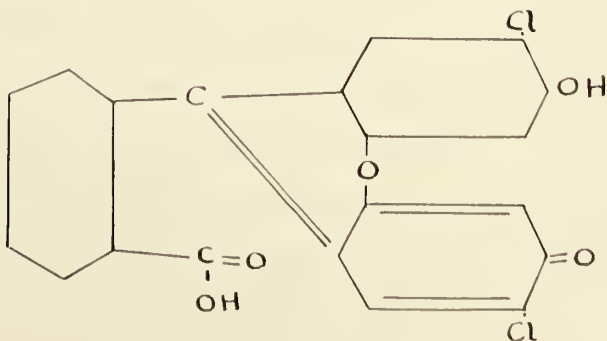




After this compound was recrystallized from hot glacial acetic acid three times, pure dichlorofluorescein was obtained, having the lactoid structure:-

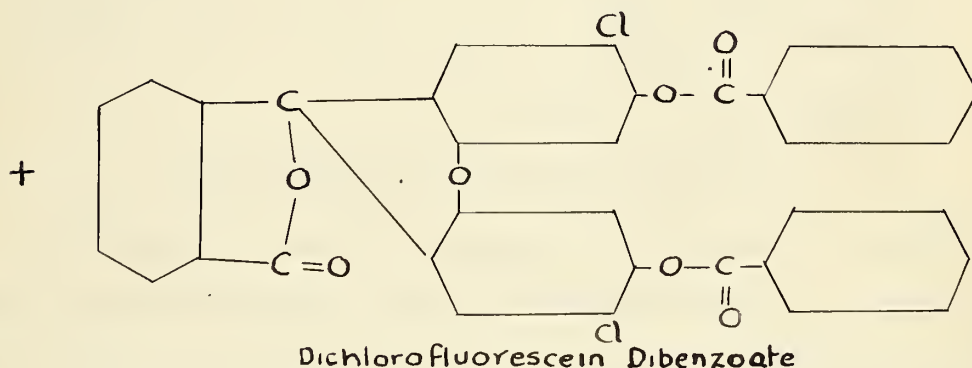
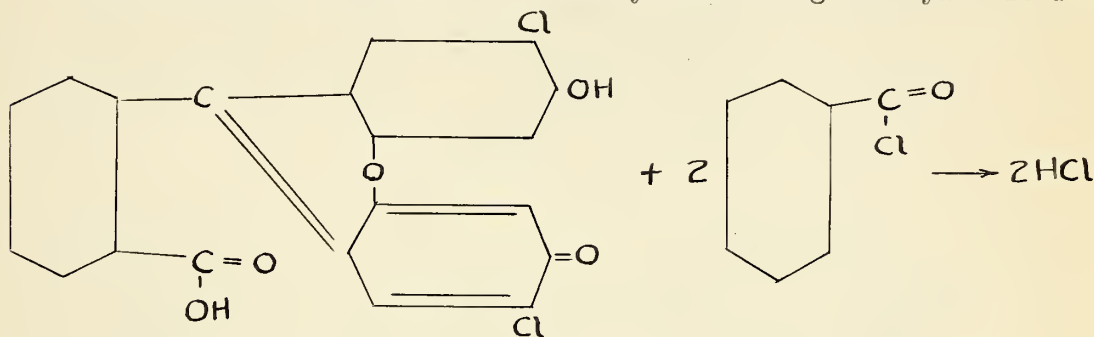


Upon heating to 275 - 300°, the above lactoid structure was transformed into the red quinoid modification:-



That dichlorofluorescein contains two phenolic groups was shown by the fact that it formed the colorless diacetate, secured in its purification, and the colorless dibenzoate.

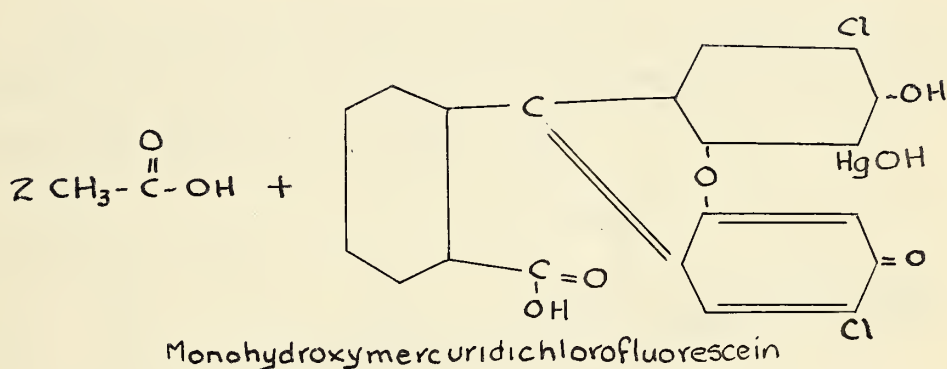
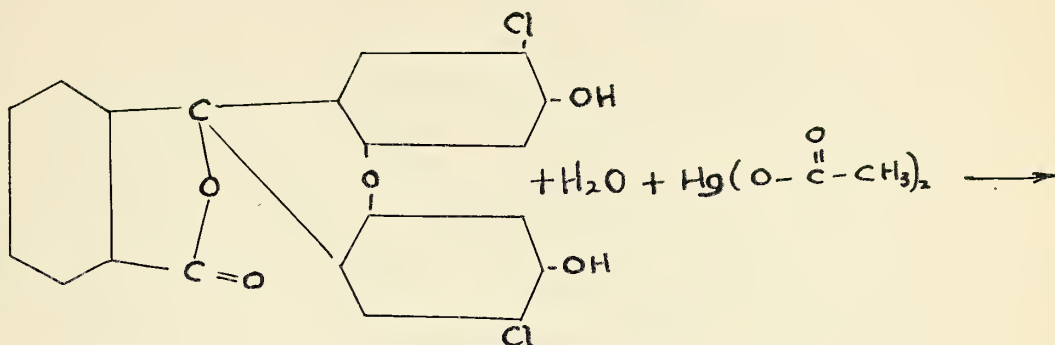
Crude dichlorofluorescein was benzoylated using benzoyl chloride.



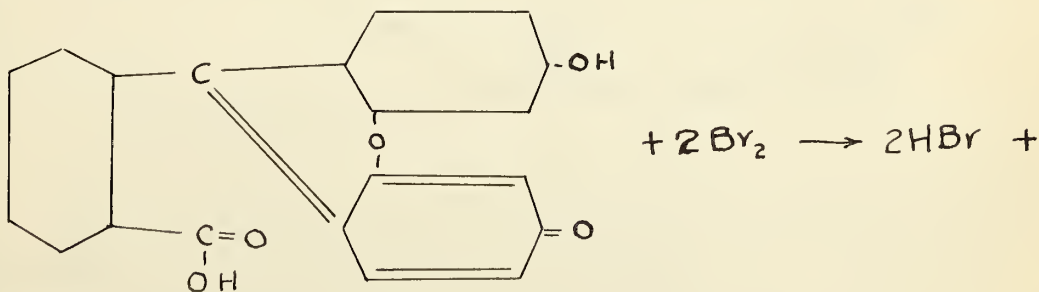
There was an addition of four molecules of ammonia to dichlorofluorescein, when dry ammonia gas was allowed to react with the pure compound.

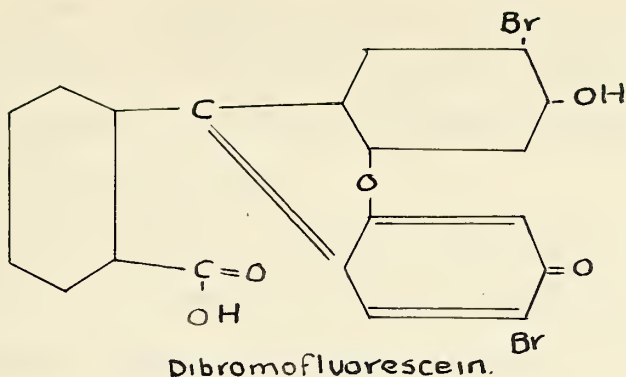
The dichlorofluorescein, so prepared from the diacetate by saponification, and recrystallization from glacial acetic acid, was mercurated according to the method of White⁶.

6. Edwin C. White, J. Am. Chem. Soc., 42, 2355 (1920).

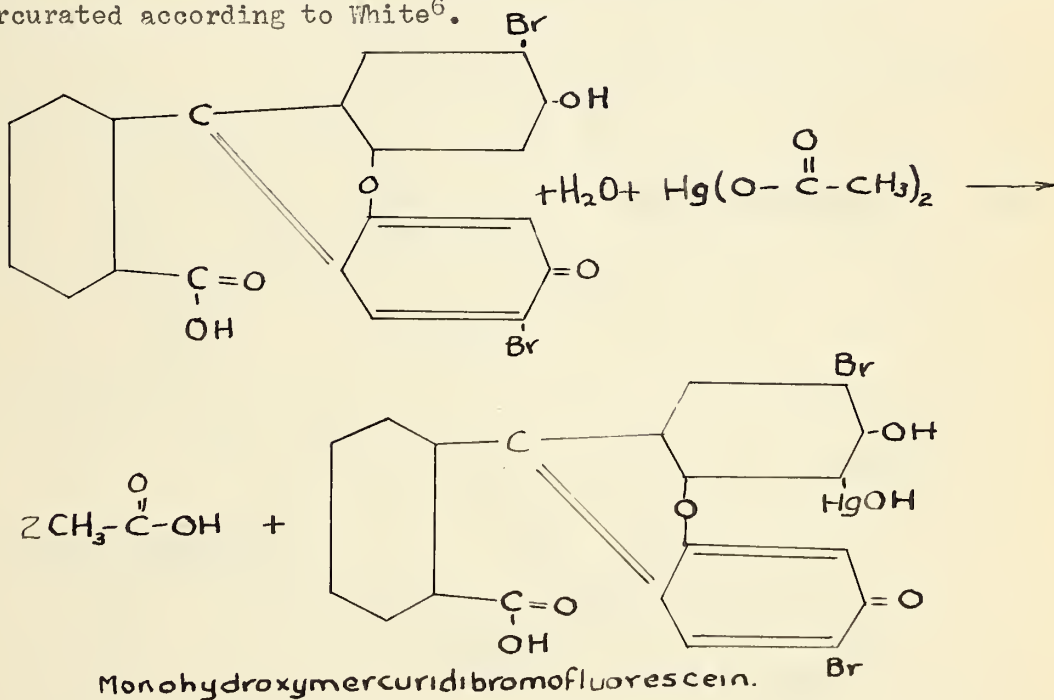


Fluorescein, prepared according to the method of Orndorff⁴ was brominated directly to give dibromofluorescein. Bromination was carried out by the addition of the calculated amount of bromine in glacial acetic acid to the suspension of fluorescein in glacial acetic acid.





The dibromofluorescein, prepared in this manner, was pure enough to convert directly to the mono-mercury derivative. It was mercurated according to White⁶.

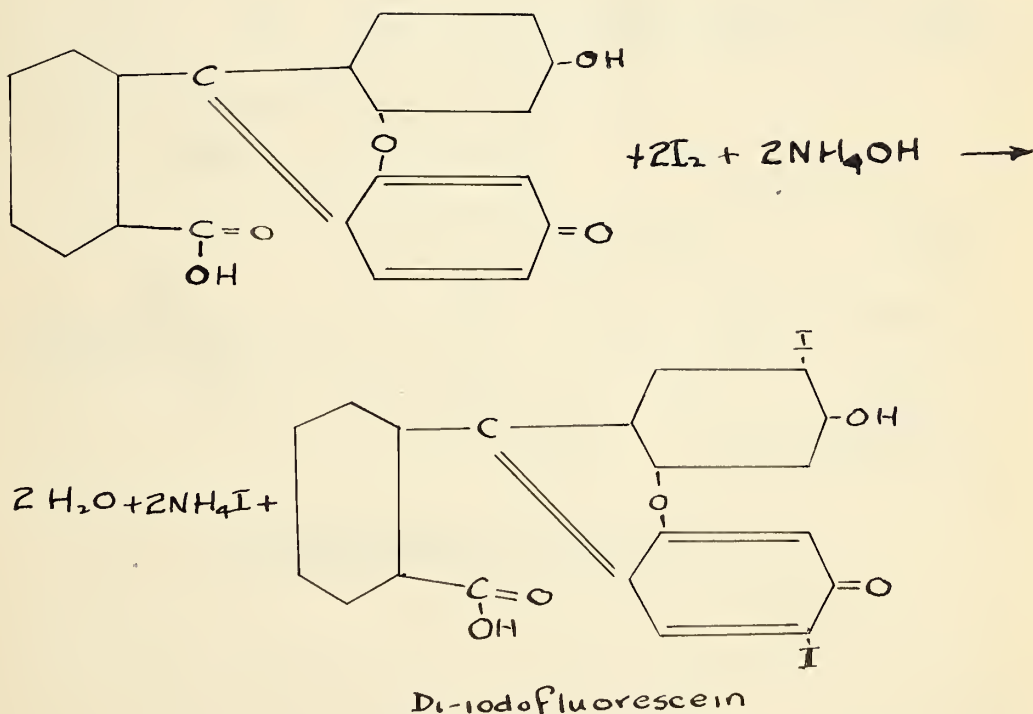


In the preparation of di-iodofluorescein an attempt was made to prepare it by the method used by Gomberg⁵ in his research on tetra-iodofluorescein. This procedure failed because of the

inability to find a suitable solvent for the diacetate.

It was finally prepared by the direct iodination of fluorescein as adopted from Rasik Lal Datta and Nogendra Prasad⁷'s work on the iodination of phenolphthalein.

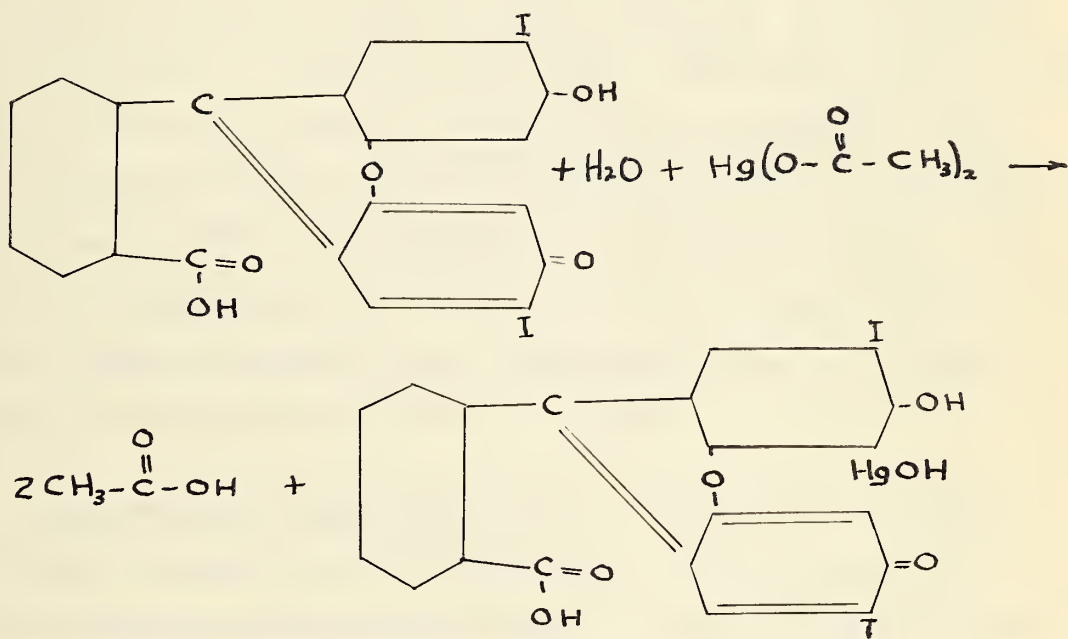
If two gram molecules of iodine, in potassium iodide, was allowed to act on an ammoniacal solution containing one gram molecule of fluorescein, a compound was formed in which the iodine content was about four per cent too low for pure di-iodofluorescein. Therefore two and one half gram molecules of iodine was used.



7. Rasik Lal Datta and Nogendra Prasad,
J. Am. Chem. Soc., 39, 441 (1927).

It was very interesting to find that regardless of the amount of excess iodine added only di-iodofluorescein was secured; in fact, with a fifty percent excess iodine used, no greater iodination was found.

The di-iodofluorescein secured in this manner was pure enough to mercurate directly. This was done by the method of White⁶.



Monohydroxymercuridi-iodo fluorescein

EXPERIMENTAL PART

Preparation of Monochlororesorcinol. - One hundred grams, (0.7 mole.) of resorcinol was dissolved in 360 g. of ether. This solution, placed in a 2-liter round-bottomed flask fitted with an efficient reflux condenser, was then treated with 120 g. (0.9 mole., an excess) of sulphuryl chloride (added dropwise). This operation was carried out in a well-ventilated hood. After the addition of sulphuryl chloride the ether was distilled off on a hot-plate. After the low-boiling material had been removed completely the temperature was raised to 257° , the boiling-point of monochlororesorcinol. The distillate which boiled at this temperature was collected and purified. Monochlororesorcinol was recrystallized from benzene until a constant melting point of 84° was obtained.

Preparation of Dichlorofluorescein. - Fifty grams (0.3 mole.) of phthalic anhydride mixed intimately with 95 g. (0.7 mole.) of monochlororesorcinol was heated to 160° in a 400 cc. beaker by means of an oil-bath. Twenty-five grams of anhydrous zinc chloride, finely ground, was then added with constant stirring during a period of thirty minutes. The temperature was then raised to $175-180^{\circ}$ and maintained for about six hours. After cooling, the reaction product was then boiled for twenty to twenty-five minutes in dilute hydrochloric acid (100 cc. of concentrated acid to 200 cc. of water) and filtered. A dark-red precipitate was secured.

This precipitate was dissolved at room temperature in an aqueous solution of sodium bicarbonate, filtered, heated to boiling and then acidified with hydrochloric acid (approximately .4N). After cooling and filtering, the precipitate was refluxed with acetic anhydride for a period of six to seven hours (2 g. of crude dichlorofluorescein to 10-12 cc. of acetic anhydride). The diacetate crystallized out upon cooling. It was filtered off and thoroughly washed with acetic anhydride. The above process was repeated four or five times. The diacetate (almost colorless) was finally purified by repeated recrystallization from benzene until a constant melting point of 237° (uncorr.) was obtained. About four or five times was found to be sufficient. After drying for several hours at 100° it was analysed for chlorine.

Anal. Calcd. for $C_{24}H_{14}O_7Cl_2$: Cl, 14.64. Found: Cl, 14.41; 14.43.

The diacetate secured as above was then saponified by refluxing 2-3 g. with alcoholic potassium hydroxide (6-7 g. of base in 40 cc. of alcohol) for three hours. Water was then added, the solution transferred to a distilling flask and the alcohol removed by distillation. The solution was then filtered, heated to boiling and acidified with hydrochloric acid. The precipitate of dichlorofluorescein so secured was dark-red in color. This dichlorofluorescein, being invariably low in chlorine even when heated to 175° , was dissolved in the minimum amount of glacial acetic acid, filtered, and then evaporated until the appearance of crystals were noted. Upon

cooling, finely-divided light-colored crystals were formed. The above process was repeated three times. After drying in an air oven at 100° for several hours the crystals were analyzed.

Anal. Calcd. for $C_{20}H_{10}O_5Cl_2$: Cl, 17.79. Found: Cl, 17.42; 17.41; 17.37.

Preparation of Dichlorofluorescein. - The quinoid form of dichlorofluorescein was obtained on heating the above lactoid form to 275-300°. Upon reaching that temperature, glistening, well-defined, dark-red crystals were obtained.

Anal. Calcd. for $C_{20}H_8O_5Cl_2$: Cl, 17.79. Found: Cl, 17.41; 17.35.

Preparation of Dichlorofluorescein Dibenzoate. - Ten grams of the crude dichlorofluorescein was suspended in 100 cc. of benzoyl chloride and the mixture heated to boiling for half an hour. At the end of this time the compound was completely dissolved. When cold, this solution was poured into 95% alcohol, when the dibenzoate separated out. This precipitate was filtered off and recrystallized from benzene. A determination of the chlorine content on the product, heated to 100° in an air oven for four hours, showed that it was dichlorofluorescein dibenzoate. It had a melting point of 274°.

Anal. Calcd. for $C_{34}H_{18}O_7Cl_2$: Cl, 11.65. Found: Cl, 11.29; 11.47.

Action of Dry Ammonia on the Colorless Dichlorofluorescein.

A weighed quantity of dry dichlorofluorescein was placed in a

porcelain boat and a current of dry ammonia gas was passed over it. The ammonia was dried by passing it through lime, potassium hydroxide and over sodium. The substance became darker and absorbed ammonia very rapidly at first but required an hour to come to constant weight. The following results were secured.

Anal. Calcd. for $C_{20}H_{10}O_6Cl_2(NH_3)_4$: NH_3 , 14.65.
Found: NH_3 , 14.02; 14.14.

Preparation of Monohydroxymercuridichlorofluorescein. - Four grams (0.013 mole.) of dichlorofluorescein was dissolved in 2 g. of sodium hydroxide in 50 cc. of water, and diluted to 200 cc. This solution was stirred and treated with 5 cc. of glacial acetic acid. To the above prepared solution was added a filtered solution of 5 g. (.016 mole.) of mercuric acetate in 100 cc. of water. A slight excess of the theoretical amount of mercuric acetate was added due to the fact that metallic mercury was precipitated in the reaction. As the solution was boiled the precipitate of monohydroxymercuridichlorofluorescein became darker in color and more granular. Boiling was continued until a portion of the reaction mixture dissolved completely in sodium hydroxide, which showed the completion of the mercuration. It was filtered and dissolved in sodium hydroxide, thus separating it from the metallic mercury which precipitated in the boiling-process. The dye was then precipitated by acidification with acetic acid, filtered, dried for three hours at 110° and analyzed.

Anal. Calcd. for $C_{20}H_{10}O_6Cl_2Hg$: Hg, 32.10. Found: Hg, 32.10; 32.33.

Preparation of Fluorescein. - Ten grams (0.07 mole.) of phthalic anhydride mixed intimately with 15 g. (0.14 mole.) of resorcinol was heated to 160° in an erlenmeyer flask. Five grams of zinc chloride, finely ground, was then added with constant stirring during a period of fifteen minutes. The temperature was then raised to 180°, and maintained for about three hours. After cooling, the reaction product was boiled for fifteen to twenty minutes in dilute hydrochloric acid. The crude fluorescein was purified by converting it into the diacetate. It was heated to boiling for two hours with five parts of acetic anhydride. The crude diacetate thus secured by allowing the acetic anhydride solution to cool, was recrystallized repeatedly from hot acetic anhydride giving a pure diacetate having a melting point of 200°.

The alkaline solution of fluorescein obtained by saponification of the pure fluorescein diacetate with alcoholic potassium hydroxide solution, after the complete removal of all the alcohol and addition of water, was heated to boiling and precipitated with a slight excess of hydrochloric acid. The fluorescein separated as a bright red, crystalline powder. It was dried for three hours at 110° and analyzed.

Anal. Calcd. for $C_{20}H_{12}O_5$: C, 72.27; H, 3.64. Found: C, 72.2; 72.3. H, 3.89; 3.61.

Preparation of Dibromofluorescein. - A suspension of 10 g. (0.03 mole.) of fluorescein in 40 g. of glacial acetic acid, was rapidly mixed with a solution of 10 g. (0.06 mole.) of bromine in 55 g. of glacial acetic acid. All of the fluorescein dissolved and

then crystals separated from the solution. After heating for one hour at the temperature of boiling water, the mixture was poured into a large volume of water, the dibromofluorescein was filtered off, dissolved in dilute sodium hydroxide solution and precipitated with an excess of acetic acid. These crystals were filtered off, dried in an air oven at 110° for three hours and analyzed.

Anal. Calcd. for $C_{20}H_{10}O_5Br_2$: Br, 32.33. Found: Br, 32.13. 32.48.

Preparation of Monohydroxymercuridibromofluorescein. - The monohydroxymercuridibromofluorescein was prepared in the same manner as the mono-mercury derivative of dichlorofluorescein. The same precautions were taken in regard to the complete mercuriation, and in the separation of the metallic mercury precipitate from the mono-mercury derivative.

Anal. Calcd. for $C_{20}H_{10}O_6Br_2Hg$: Hg, 28.39. Found: Hg, 28.20; 28.31.

Preparation of Di-iodofluorescein. - Three and three tenth grams (0.01 mole.) of fluorescein was dissolved in concentrated ammonium hydroxide and to this solution was gradually added 6.4 g. (0.025 mole.) of iodine, dissolved in potassium iodide, while the solution was still warm. The iodine seemed to be taken up at first, but when it gradually cooled, nitrogen iodide precipitated. The solution was then neutralized with hydrochloric acid. The dye di-iodofluorescein immediately precipitated out of solution. It was filtered, dried at 110° for four hours and analyzed.

Anal. Calcd. for $C_{20}H_{10}O_5I_2$: I, 43.49. Found: I, 42.91. 43.80.

Preparation of Monohydroxymercuridi-iodofluorescein. - The monohydroxymercuridi-iodofluorescein was prepared in the same manner as the mono-mercury derivative of dichlorofluorescein. The same precautions were taken in regard, to the complete precipitation, and in the separation of the metallic mercury precipitate from the mono-mercury derivative.

Anal. Calcd. for $C_{20}H_{10}O_6I_2Hg$: Hg, 25.05. Found: Hg, 25.33; 25.21.

SUMMARY

1. Pure dichlorofluorescein has been prepared and proved to exist in two isomeric forms, quinoid and lactoid, having the formula $C_{20}H_{10}O_5Cl_2$.
2. The colorless diacetate and dibenzoate of dichlorofluorescein have been prepared showing the lactoid structure.
3. A new method for the preparation of di-iodofluorescein has been outlined.
4. The mono-mercury derivatives of dichloro, dibromo and di-iodofluorescein have been prepared.

PART 2

PREPARATION OF β -AUROTHIOGLYCERIC ACID ETHYL ESTER

Gold has been used as a drug for many centuries. Abu Moussa Gafar¹ recommended gold in the middle of the eighth century as a remedy for administration to human beings, animals and plants, but gold compounds have been developed to a great extent only in more recent years.

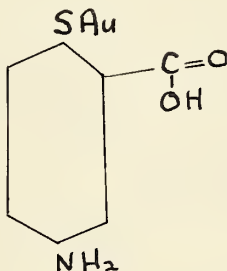
Robert Koch² (1890) found that gold cyanide, auro and auri cyanide $\text{Au}(\text{CN})$ and $\text{Au}(\text{CN})_3$ inhibited the growth of the tuber bacilli in a dilution of 1 : 2,000,000, but Bruck and Glueck³ found that it also caused severe poisoning effects on the walls of the cells.

In 1914, Spiess and Feldt⁴ brought out a new remedy; recognizing the high toxicity of gold cyanide on the one hand and its healing effect on tuberculous organs on the other, they tried to find a carrier which would decrease its toxicity. They used cantharidin which has a marked affinity for tubercular organs. In order to decrease the toxicity of cantharidin, they combined it with ethylene-

1. Abu Moussa Gafar, Healing Art, 145, (1887).
2. Robert Koch, Deutsche Med. Wochenschrift, 757, (1890).
3. Bruck and Gluick, Muenchener Med. Wochenschrift, 60, 57, (1913).
4. Feldt and Spiess, Berliner Klenische Wochenschrift, 220 - 223, (1918).

diamine, by which combination the toxicity was lowered 700 times. This combination called "Aurocantan" was found to be less poisonous than gold cyanide and represented a marked advance in the treatment of tuberculosis.

A still better and less toxic gold compound was prepared in 1917. Feldt and Spiess⁴ once more introduced a new gold preparation in which gold was introduced into an organic compound, namely "KrySolgan," the gold-sodium salt of an aminothiophenol carbonic acid.

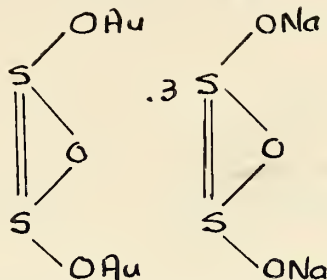


At the present time it is manufactured by Hoechst Farbwerke and is available in German markets. Feldt pointed out that "KrySolgan" acts as a catalyst only and as such is used in very small doses.

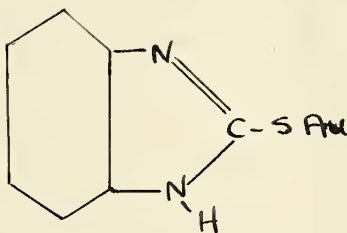
In 1924 Professor Mollgaard⁵ of Copenhagen, Denmark introduced another gold compound which he called "Sanocrysin." Chemically speaking, it is gold-sodium thiosulphate, a complex gold salt, in which the gold is in the aurous or monovalent form.

5. Mollgaard "Chemotherapy of Tuberculosis," Copenhagen, Denmark.

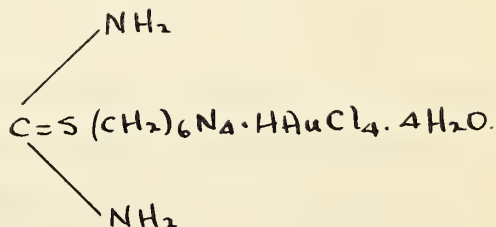
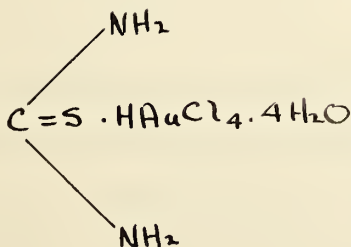
"Sanocrysin" has the structural formula somewhat like this:-



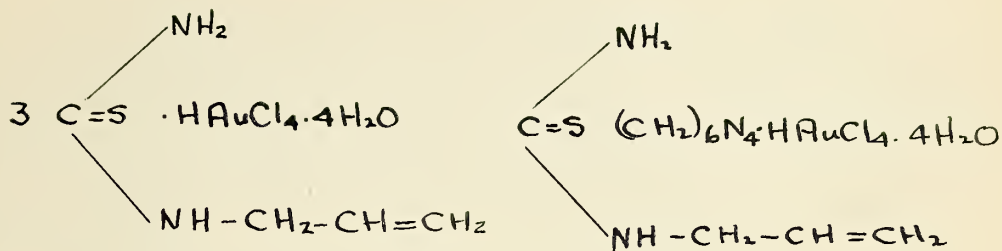
In 1925 another gold compound was discovered in connection with the treatment of tuberculosis, namely "Triphal". This compound is the gold-sodium salt of thiobenzimidazolcarbonic acid of the following formula:-



Some gold salts of thiourea and thiosinamine were prepared by H. Brown⁶. They have the following structure.



6. H. Brown, Archives of Dermatology and Syphilology, 13, 43, (1926).



These gold salts (1 and 3) were found to be water insoluble but the addition of these compounds with hexamethylenetetramine (2 and 4) proved soluble in water. It might be well to emphasize here that no gold salt of urea or alkyl urea has so far been known. The presence of sulphur seems to be essential for the formation of gold salts.

Very recently, however, M. Kharash and H. S. Isbell⁷ succeeded in preparing compounds containing carbon-gold linking. The method which they have elaborated is as follows:-

Anhydrous gold chloride is prepared by evaporating a solution of the commercial hydrochlorauric acid to dryness, then heated to 160°C. Then a dry current of chlorine is passed over it and finally dried in a current of air. This anhydrous gold chloride is treated with benzene, the reaction allowed to proceed for only 60 to 90 seconds and is arrested by the addition of ether. The precipitate thus obtained is recrystallized from alcohol. It represents phenylauri-dichloride and the following reaction takes place:-

7. M. Kharash and H. S. Isbell. J. Am. Chem. Soc., 53, 3053 (1931)



It is a yellow substance insoluble in water. Instead of benzene, naphthalene, diphenyl or toluene can be used. The disadvantage of the gold compound thus obtained lies in the fact that they are water insoluble.

German investigators of recent date point out that the gold-sulphur linking offers the best chance for the formation of gold compounds which are therapeutically of importance.

It was thought then that the gold derivative of β -aurothioglyceric acid ethyl ester might have therapeutic properties, because it contains the gold-sulphur linkage, one of the prerequisites according to the European investigators. This is then a method for the preparation of β -aurothioglyceric acid ethyl ester.

β -Thioglyceric acid ethyl ester was prepared according to the method of C. Frederick Koelsch⁸. Glycerol α -monochlorohydrin prepared according to J. B. Conant and O. R. Quayle⁹ was treated

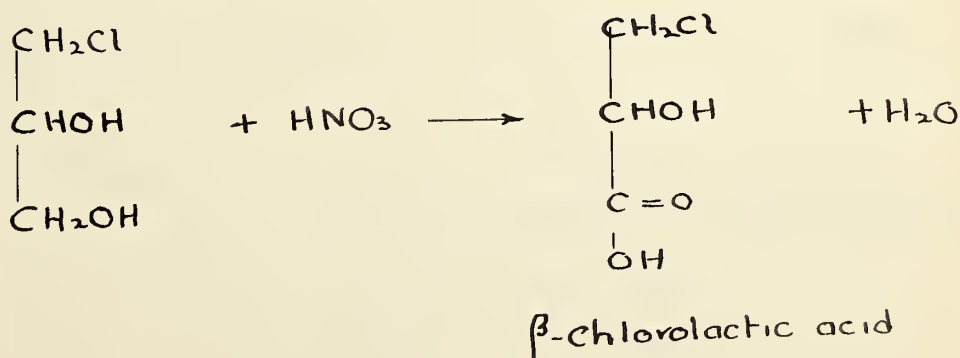
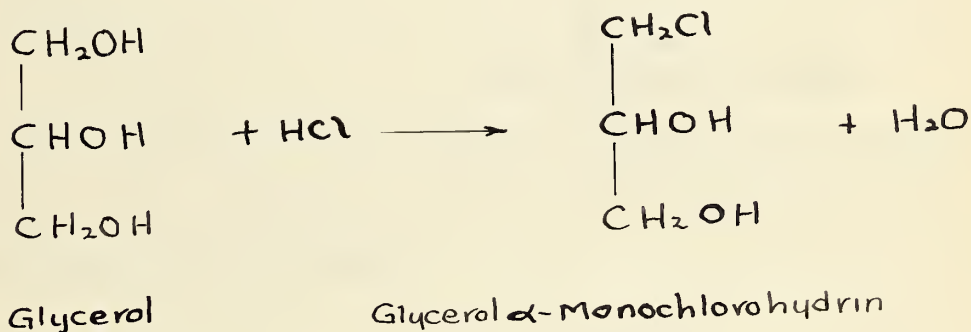
8. C. F. Koelsch, J. Am. Chem. Soc., 52. 1105 (1930).

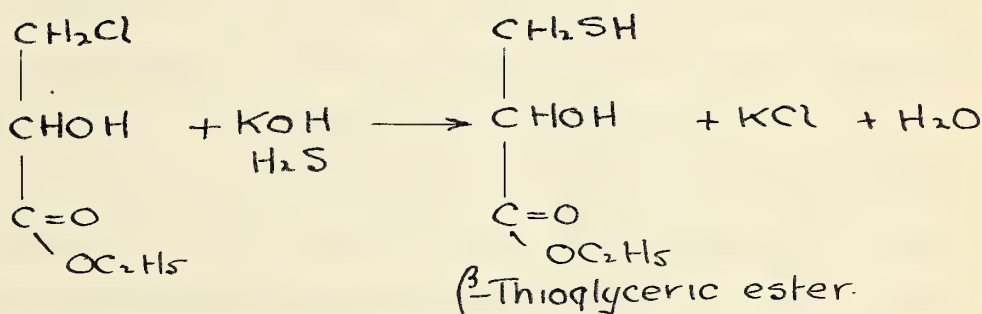
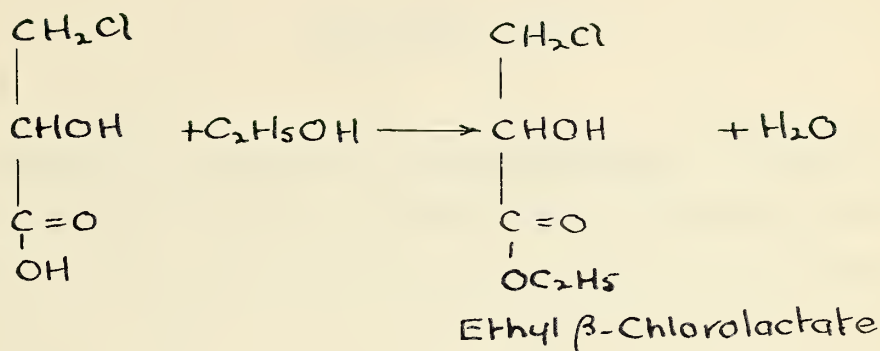
9. J. B. Conant and O. R. Quayle Organic Syntheses. Vol. 2, p. 33.

with nitric acid as the oxidizing agent, yielding the β -chloro-lactic acid. It was then converted to the ester by refluxing with absolute alcohol, yielding ethyl β -chlorolactate, which compound was treated with an alcoholic potassium hydroxide solution saturated with hydrogen sulphide gas, yielding the β -thioglyceric acid ethyl ester.

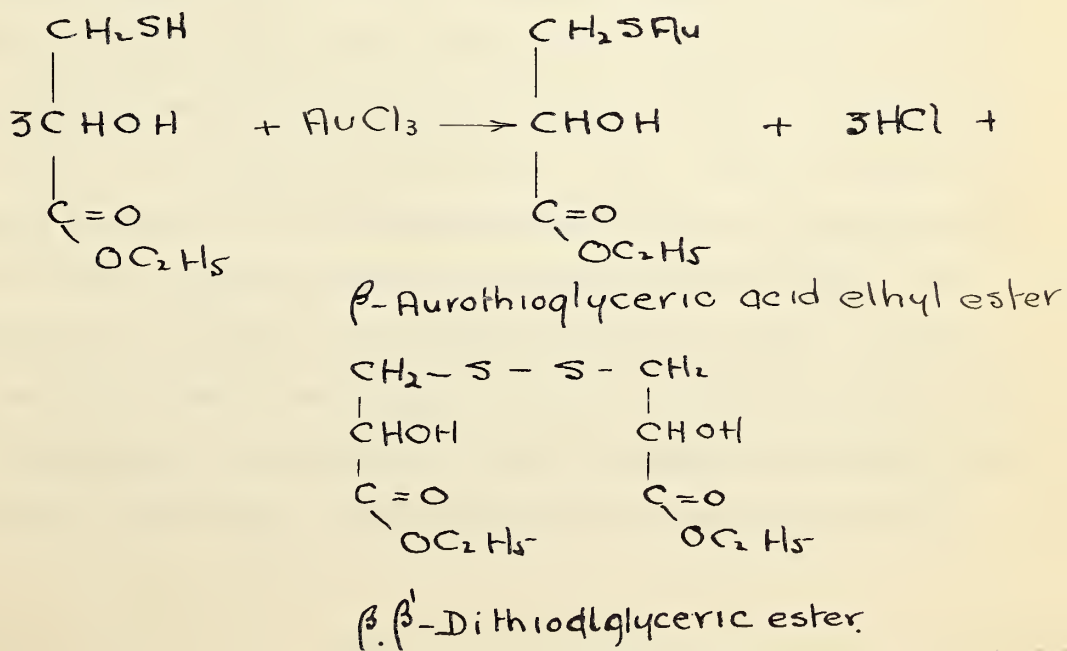
Regardless of the precautions taken only the poorest yields resulted.

The reactions are given below:-





The auro derivative was obtained by adding a methyl alcohol solution of gold chloride to a solution of β -thioglyceric acid ethyl ester in methyl alcohol.



EXPERIMENTAL PART

Preparation of Glycerol α -Monochlorohydrin. - Five hundred grams of glycerol and 10 g. of glacial acetic acid were mixed in a weighed 1 - liter flask, which was placed in an oil-bath heated to 105 - 110°. A rapid stream of dry hydrogen chloride was introduced into the mixture. The flask was removed from the bath from time to time and reweighed. At the end of about four hours the flask gained 190 g. in weight. The reaction was then complete.

The product was distilled under reduced pressure. Below 114° at 14 mm., 220 - 250 g. distilled; this portion was mostly water. The α - monochlorohydrin was collected between 114 - 120° at 14 mm. It weighed 360 g. which was 66 percent of the theoretical amount.

Preparation of β -Chlorolactic Acid. - In a 1,000 cc. measuring cylinder, fitted with a dropping funnel the lower end of which extended to within 2 mm. of the bottom, was placed a mixture of 250 g. of glycerol α -monochlorohydrin with 250 g. of water. In the dropping funnel was placed 350 g. of nitric acid. The nitric acid was allowed to flow into the chlorohydrin-water mixture in portions of about 20 cc., care being taken not to mix the layers formed. The addition was regulated so that there was always a layer of nitric acid at the bottom of the cylinder, 5 - 10 cc. thick. A bright green color developed at the junction of the two layers, and slowly spread throughout the mixture. When all the acid had been added, which

usually required two days, the mixture was allowed to stand until it had become colorless and no more oxides of nitrogen were evolved, requiring some eight to ten days longer.

The mixture was then transferred to a 1 - liter Claisen flask and the water and most of the excess nitric acid were distilled off under reduced pressure (25-30 mm.). The residue (230-240 g.) which became crystalline on standing, was pure enough for conversion to the ester.

Preparation of Ethyl β -Chlorolactate. - Crude β -chlorolactic acid freed of water and nitric acid, was dissolved in twice its weight of absolute alcohol containing 4 % of hydrogen chloride and the solution was refluxed for four hours. The alcohol was distilled off from a hot-plate, and the residue distilled under reduced pressure. After two distillations the ester was obtained as an oil boiling at 106-108° at 25 mm., which solidified to a mass of colorless needles melting at 35-37° (uncorr.).

Preparation of β -Thioglyceric Acid Ethyl Ester. - A solution of 100 g. of potassium hydroxide in 560 cc. of 95% alcohol, contained in a 1-liter 3-necked flask fitted with a stirrer and with a thermometer dipping into the liquid, was saturated at room temperature with hydrogen sulphide. To this was added about 20 cc. of a solution of 150 g. of ethyl β -chlorolactate in 185 cc. of alcohol. The mixture was warmed to 60-65°, at which temperature the reaction started, as was evidenced by the separation of potassium chloride.

The temperature of the mixture was kept at 65-70° by the slow addition, with stirring, of the remainder of the ethyl β -chloro-lactate solution. When the addition was completed, the mixture was heated at 70° with stirring for thirty minutes. The mixture was then cooled and dry hydrogen chloride was passed in until the mixture was acid to congo-red. The potassium chloride was filtered off and the alcohol was distilled from the filtrate. The residue was distilled under reduced pressure, giving crude ethyl β -thioglyceric acid ethyl ester boiling at 113-120° at 19 mm. It was redistilled and only that boiling between 113-114° at 19 mm. was collected.

Preparation of β -Aurothioglyceric Acid Ethyl Ester. - Six and one tenth grams (.02 mole.) of auric chloride in methyl alcohol was added to a solution of 9.0 g. (.06 mole.) of β -thioglyceric acid ethyl ester in methyl alcohol. Immediately a white horny-like mass precipitated. It was washed with methyl alcohol and carefully dried for three hours in a 100° oven and analyzed.

Anal. Calcd. for $C_5H_9O_3SAu$: Au, 56.95. Found: Au, 56.4; 56.4; 56.2; 56.1.

SUMMARY

1. β -Aurothioglyceric acid ethyl ester has been prepared.

POSTSCRIPT

In the majority of compounds described no melting points are given, because they do not melt at temperatures below 350°. Also no yields are mentioned for the metallic derivatives, the yields obtained for these compounds under the conditions of their preparation are quantitative yields.

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